# MODIFICATION BY PRE-EXISTING COMORBIDITIES OF THE EFFECT OF ADHERENCE TO A LUNG-PROTECTIVE MECHANICAL VENTILATION STRATEGY IN A COHORT OF PATIENTS WITH THE ACUTE RESPIRATORY DISTRESS SYNDROME

by
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**Abstract**

**Statement of the problem:** Literature suggests that the incidence of and outcomes following Acute Respiratory Distress Syndrome (ARDS) vary with the presence of certain chronic comorbidities, possibly due to alterations in the innate immune system. We sought to determine whether the association of lung-protective ventilation (LPV), defined by tidal volumes ≤6.5 ml/ kg predicted body weight and plateau pressures ≤30 cm $H_2O$, with ICU survival was modified by the presence of certain comorbidities.

**Methods:** Multi-variable, time-varying Cox regression analysis of a multisite, prospective cohort study of 485 patients with baseline assessment of seven comorbidities potentially associated with ARDS progression. Analyses included adjustment for twice-daily assessment of tidal volume and other respiratory variables and daily assessment of other mortality predictors. Effect modification between the effect of LPV and each of seven comorbidities was assessed by a statistical interaction term.

**Results:** The prevalence of comorbidities was as follows: 119 (25%) had excess alcohol use histories, 112 (23%) diabetes, 69 (14%) HIV disease, 51 (11%) injection drug use within past 30 days, 48 (9.9%) moderate or severe liver disease, 42 (8.7%) hematologic malignancy history, and 36 (7.4%) rheumatologic disease. The adjusted hazard ratio (HR) for mortality for each 12-hour period of LPV-ventilation was 0.96 (95% CI: 0.93-1.00; p=0.041). Only hematologic malignancy demonstrated a significant interaction (p=0.039 for interaction) with LPV, with HRs for each 12-hour period with LPV in patients with vs. without this comorbidity of 1.03 (95% CI 0.94-1.12) and 0.96 (95% CI 0.93-1.00), respectively.

**Conclusions:** There was limited support for the hypothesis that LPV's protective effect may be modified by the presence or absence of certain comorbidities present before ARDS onset. Of seven comorbidities tested only a history of hematologic malignancy demonstrated a significant interaction with the effect of LPV adherence, with LPV having no protective effect in patients with this comorbidity.

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## Introduction

Acute respiratory distress syndrome (ARDS) is a common and often lethal disease process in the intensive care unit (ICU). ARDS generally occurs shortly after an inciting acute event, such as trauma, pulmonary- or non-pulmonary sepsis, or pancreatitis.[1] The "two-hit hypothesis" of ARDS pathophysiology[2,3] proposes that ARDS develops as the result of a second mechanical, chemical, or biological insult to the lung in the setting of an already vulnerable host inflammatory milieu. For example, ARDS may develop during mechanical ventilation following severe trauma at a site distant from the lung or following a unilateral pneumonia. Lung injury may be initiated primarily by innate immune system pathways via pattern recognition receptors (PRRs) directed either toward foreign structures (referred to as pathogen-associated molecular patterns (PAMPs)), such as bacterial lipopolysaccharide, or to intrinsic markers of cell damage (referred to as damage-associated molecular patterns (DAMPs)), such as native high-mobility group box 1 protein.[4,5] PRR activation then stimulates toll-like receptor (TLR) pathways in macrophages and other sentinel immune cells contributing to further inflammation and multi-organ failure.[4,5]

Certain chronic diseases may alter a patient's risk for developing ARDS following an inciting acute insult and/or their likelihood of then surviving subsequent ARDS.[6] In most of these chronic disease states, the biochemical mechanisms underlying these observations are poorly understood. However, chronic alcohol abuse is a relatively well-described model of how a pre-existing comorbidity might influence ARDS progression. Chronic alcohol abuse is known to increase the risk for developing ARDS[7] and the absolute risk of death after ARDS onset[8,9] by altering the redox state of cells via alterations in glutathione and free-radical metabolism thus making the cells more susceptible to inflammatory injury.[10,11] Other chronic disease states also have shown increased risk for developing ARDS and/or increased risk-adjusted mortality after ARDS onset, including HIV disease,[12-14] hepatic cirrhosis,[12, 15-18] injection drug abuse,[19] auto-immune diseases[20-23] and some cancers.[24,25]

Conversely, diabetes appears to reduce the risk-adjusted odds of developing ARDS.[25-28] The differing impacts of some chronic diseases on ARDS risk has been hypothesized to result from known differences in macrophage expression of the PPAR-gamma and heme-oxygenase-1 pathways in different chronic inflammatory states.[29,30]

Patients with ARDS usually require mechanical ventilatory support. Traditionally, this was done using relatively large tidal volumes and low positive end-expiratory pressures (PEEP). This approach leads to mechanical ventilation-induced barotrauma, atelectatrauma, and biotrauma.[31-34] Subsequent randomized controlled trials and meta-analyses of ARDS have demonstrated that a volume- and pressure-limited lung protective mechanical ventilation (LPV) strategy, with algorithmically-titrated PEEP, reduces short-term mortality.[35-39] Other studies have demonstrated release of DAMPs with mechanical ventilation[40] and variations in inflammatory markers of ARDS with different mechanical ventilation strategies.[41,42] Other researchers have reported reductions in inflammatory markers and neutrophil activity with an LPV strategy in both animal models[43,44] and patients with ARDS.[45] These observations suggest that LPV may act, at least partly, by modifying the underlying immunologic processes that initiate and propagate ARDS.

Given this evidence, we hypothesized that the association between LPV and short-term survival would differ according to a patient's comorbid disease state prior to ARDS onset.

## Methods

We enrolled 520 consecutive eligible patients with ARDS into an institutional review board (IRB)-approved prospective cohort study conducted between 2004 and 2007. These patients were being treated in 13 medical, trauma, and surgical ICUs at four Baltimore, Maryland academic medical centers. For inclusion, patients were required to be mechanically ventilated and meet the American-European consensus criteria for acute lung injury.[46] The American-European consensus criteria were the diagnostic criteria in effect at the time of enrollment. Consistent with the more current Berlin consensus recommendations,[47] we use the term ARDS rather than acute lung injury to describe this cohort. IRB approval was obtained from all participating sites with a waiver of informed consent granted for abstraction of preexisting data from the medical record.

Patients were ineligible for enrollment if they were managed in an ICU specializing primarily in neurologic diseases or were patients with acute lung injury with primary neurologic disease or head trauma. Patients were also excluded from enrollment if they had a physician order limiting life support (other than a sole "do not resuscitate order"), life expectancy <6 months, baseline communication limitations or cognitive deficits, lacked a fixed follow-up address, were transferred from an outside facility with ALI duration > 24 hours, were mechanically ventilated > 5 days prior to ALI development, or had history of lung resection. Patients also were excluded from this analysis if they had no "eligible" ventilator settings (as subsequently defined) or if they lacked a recorded height, both preventing assessment of adherence to LPV strategies.

### Assessment of lung protective ventilation (LPV)

Mechanical ventilation settings and key ventilator measurements were recorded daily at 06:00 and 18:00 for the duration of the patient's mechanical ventilation. A given ventilator setting was considered "eligible" for LPV if mechanical ventilation was provided via an artificial airway and if the FiO2 was either ≥ 50% or if the positive end expiratory pressure (PEEP) was >5 cm of

water. We chose this definition because it approximated the threshold at which the ARDS Network ventilation protocol permitted trials of spontaneous breathing in which tidal volume and plateau pressure were not specified and discontinuation of mechanical ventilation could be evaluated. A given ventilator setting was considered "adherent" to LPV if tidal volume was ≤ 6.5 cc/ kg predicted body weight (PBW, the threshold used in the ARDS Network tidal volume trial to designate study site adherence to the goal tidal volume of ≤6.0 mL/kg PBW), and plateau pressure ≥30. For patients in pressure-regulated modes, the plateau pressure was approximated using the peak pressure or the sum of the PEEP plus the prescribed increment in inspiratory pressure.

All ventilator settings using airway pressure release ventilation (APRV) and high frequency oscillatory ventilation (HFOV) modes could not be assessed for adherence with LPV, but use of each of these two ventilator modes was considered in the analysis as time-varying covariates.

Assessment of primary outcome: survival during the initial ICU stay

Survival until discharge from the index ICU admission for ARDS was selected as the primary outcome because of its temporal proximity to the primary exposure.

Assessment of baseline comorbidities

Baseline comorbidities were selected *a priori,* based on prior literature suggesting that their presence might alter the incidence of or death from ARDS. These comorbidities, evaluated as effect-modifiers of the association of LPV and ICU survival, were: HIV disease, excessive alcohol use, current injection drug use, moderate or severe liver disease, rheumatologic disease, prior or active hematologic malignancy, and diabetes. These comorbidity data were obtain from medical records, with the Charlson comorbidity index definitions[48] used to define HIV disease, moderate and severe liver disease, rheumatologic diseases, hematologic malignancy, and diabetes. Excess alcohol use was defined as current or prior alcoholism, alcohol abuse, problem drinking,

alcoholic cirrhosis, or alcoholic liver disease. Current injection drug use was defined as injection or intravenous drug use within the past thirty days or specifically documented as “active" in the medical record.

Assessment of baseline exposures

Baseline exposures included patient characteristics and hospital admission diagnosis category, as obtained from medical records. The following baseline exposures were included in the analyses: age, sex, body mass index (BMI) category, comorbidity burden (Charlson index),[48] severity of illness within 24 hours of admission to the ICU (APACHE II score)[49] and admission SOFA organ failure score,[50] ARDS risk factor (non-pulmonary sepsis vs. all others), ICU type (medical vs. surgical), and ICU admission source (emergency department vs. all others). Study site was also included in the model as a categorical variable. Sites 3 and 4 were combined, as Site 4 had a small sample size and they shared ICU physician staffing patterns and had similar crude mortality hazard ratios.

Assessment of time-varying covariates

Time-varying covariates were collected once or twice daily beginning at ARDS onset and continuing for the duration of the patient’s mechanical ventilation and/ or ICU stay as appropriate. Covariates measured once daily were: delirium status (Confusion Assessment Method for the ICU (CAM-ICU))[51], sedation status (Richmond Agitation and Sedation Scale (RASS)),[52] receipt and dose of systemic corticosteroids, and daily net fluid balance (total fluid input minus total fluid output). Ventilation parameters included in the model, collected twice daily at 06:00 and 18:00, were: PaO2, arterial pH, actual respiratory rate, static compliance of the respiratory system, FiO2, positive end-expiratory pressure, and the use of APRV, HFOV, paralysis, or prone positioning during the preceding 12 hour period.

Missing data

There were no patients with missing outcome or other patient-level data. Less than 0.2% of the collected ventilator setting and arterial blood gas data was missing. Approximately 10% of the plateau pressure values, required to calculate static compliance of the respiratory system, were missing, as were 16% of the RASS values and 25.7% of the CAM-ICU values. Multiple imputation was used to impute each of these measurements, creating 5 complete datasets; Rubin's method was used to pool the results across the imputed datasets.[53,54]

Statistical analysis

The key explanatory covariates were summarized and statistically compared using Fisher's exact test or the non-parametric K-sample test of the equality of medians as appropriate. A multivariable time-varying Cox proportional hazards regression model was used to estimate the hazard ratios as a function of exposure to lung protective ventilation, the comorbidities of interest included in the model simultaneously, and the additional baseline exposures and time-varying covariates chosen a-prior for clinical relevance. The primary exposure was modeled continuously as the time varying number of ventilator settings adherent to LPV with adjustment for the total duration of mechanical ventilation. A robust (Huber-White sandwich) variance estimate was used. The Efron method was used to handle ties.[55,56] Within this multivariable time-varying Cox regression model including all of the comorbidity main-effects, statistical interactions between each of the binary indicators of the comorbidities with the continuous LPV-adherence variable were separately assessed (i.e., a single comorbidity*LPV-adherence interaction term was present in the model). The hazard ratios for the effect of LPV-adherence on survival in patients with and without the comorbidities were calculated.

For continuous covariates, Martingale residual plots were created to confirm appropriate modeling, with no departures from linearity detected. Variance inflation factor analysis confirmed no significant multicollinearity in the multivariable model. The proportional hazard

assumption was tested using a test for trend and evaluation of graphical displays of Schoenfeld residuals.

All statistical analyses were performed using STATA 13.1 (StataCorp, College Station, TX). All tests of statistical significance used a two-sided P value $<0.05$.

**Results**

Of the 520 patients enrolled in the study, 32 (6%) had no eligible ventilator settings and three (0.6%) had missing height and were excluded from analysis (Figure 1). The remaining 485 patients were on mechanical ventilation via an artificial airway during a total of 12,760 12-hour observation intervals. Mechanical ventilation during 7112 (55.7%) of these intervals was eligible for LPV, and during 2548 (36%) of these intervals the ventilator settings were observed to be adherent to LPV.

Among the 485 patients included in the analysis, the median (IQR) age was 53 (42-63) years, 57% were male, and 38% were admitted from the Emergency Department (ED) (Table 1). Most (85%) were admitted to a MICU, and 30% had non-pulmonary sepsis as the primary risk factor for ARDS (Table 1). The median (IQR) baseline APACHE II was 27 (20-33).

With respect to comorbidities, 25% of patients had a recorded history of alcohol abuse and 11% had abused drugs via injection within the past month. Only 6.2% were reported to have no chronic comorbidities (Table 2).

In terms of ICU exposures (Table 3), the median (IQR) duration of mechanical ventilation 9 (5-17) days, 24% of patients ever received neuromuscular blockade, 3.5% were ever proned, 13% were ever on APRV ventilation mode and 12% were ever on HFOV ventilation mode. The median (IQR) ICU and hospital lengths of stay were 11 (6-18) and 21 (13-36) days, respectively. During their initial ICU stay 199 patients (41%) died.

Table 4 presents the crude and adjusted hazard ratios for mortality during the index ICU admission as a function of LPV adherence, the comorbidities of interest and the remaining adjustment variables including duration of mechanical ventilation. After adjustment for the 26 explanatory covariates and LPV adherence, rheumatologic comorbid disease was significantly

associated with an increased hazard of ICU mortality (HR 2.65; 95% CI 1.40-5.02) (p = 0.003). Consistent with prior literature, the adjusted hazard of mortality was lower among patients with diabetes relative to those without (HR 0.45; 95% CI 0.20-1.02) (p = 0.056); however, this result was not statistically significant. The presence of HIV disease (HR 0.95; 95% CI 0.49-1.83) (p=0.876), current or prior excessive alcohol use (HR 0.96; 95% CI 0.59-1.55) (p=0.863), current injection drug use (HR 1.08; 95% CI 0.53-2.19) (p=0.827), hematologic malignancy (HR 0.77; 95% CI 0.50-1.17) (p=0.217), or moderate or severe liver (HR 0.80; 95% CI 0.44-1.46) (p=0.474) did not confer a statistically significant increased adjusted hazard of ICU death.

There was a non-significant statistical interaction (p=0.074) between the presence of rheumatologic disease and LPV-adherence (Table 5). A history of hematologic malignancy demonstrated a statistically significant interaction (p = 0.039) with LPV adherence. The hazard ratios for the effect of each 12-hour period with LPV-adherence (accounting for the main-effect term for LPV-adherence term plus the interaction between LPV-adherence and the presence or absence of hematologic malignancy) was higher in patients with (HR 1.03; 95% CI 0.94-1.12) versus without (HR 0.96; 95% CI 0.93-1.00) hematologic malignancy.

We were unable to detect any significant statistical interaction for the other comorbidities. However, patients with a history of excessive alcohol use, moderate or severe liver disease, and diabetes all showed a non-significant increase in the summary protective effect of LPV-adherence (i.e., a reduction in the hazard ratio for death) when compared to patients without these comorbidities (Table 5). Patients with HIV disease, current injection drug use, rheumatologic disease, or past or present hematologic malignancy did not demonstrate such an effect.

**Discussion**

Pre-clinical and clinical research have implicated innate immune system signaling pathways as playing pivotal roles in the pathophysiology associated with the development and progression of ARDS and in the pathological mechanisms of ventilator-associated lung injury.[4,5] It has also been suggested that activation of these pathways contribute to the increased morbidity and mortality associated with some chronic diseases in the setting of ARDS.[30] In a multi-site, 485-patient prospective cohort study of ARDS patients, we assessed the interaction between LPV and seven comorbidities that have been suggested in previous literature to modify the progression of ARDS, hypothesizing that the associations between LPV and short-term mortality would vary according to a patient's comorbid disease state. Our results provide limited data in support of this hypothesis.

Our study found an adjusted HR of 0.96 (95% CI 0.93-1.00) for each additional 12 hour period of LPV-adherence. Only one of the comorbidities, rheumatologic diseases (HR 2.65; 95% CI 1.40-5.02), demonstrated an independent, increased hazard of death after adjusting for the other explanatory covariates.

Hematologic malignancy was the only comorbidity that exhibited significant statistical interaction of the effect of LPV-adherence on the hazard of death (p=0.039). However, among patients with excessive alcohol use, moderate or severe liver disease, or diabetes, the hazard ratios for each additional 12 hour period of LPV adherence demonstrated statistically significant reductions in the adjusted hazard of death, while among otherwise similar patients without these diseases no such protective effect was detected, with these differences not being statistically significant (Table 5).

While we are unaware of any other literature that has attempted to assess for effect modification of LPV with comorbidities in ARDS, our findings are notable because excessive alcohol use,

moderate or severe liver disease, and diabetes are arguably the best-documented examples of chronic diseases which alter the incidence or natural history of ARDS.[12,15-18,30]

Our study has potential limitations. First, this was an observational study and therefore cannot prove causation. Second, our ability to assess for the presence and severity of comorbidities was limited by the use of medical records and existing definitions for their ascertainment. This issue limited our ability to optimally assess for comorbidity activity (e.g., active hematologic malignancy vs. a remote history of it) and limited our ability to detect any true association that might exist. Third, the prevalence of some comorbidities within this cohort was low. Moderate or severe liver disease, rheumatologic disease, and hematologic malignancy all occurred in <10% of our cohort. This issue reduced our power to detect any true effect modification for these comorbidities. Fourth, we also deliberately selected a proximal time point for our primary outcome (survival to ICU discharge). While this reduced the likelihood that our results might be obscured by deaths not directly related to ARDS, it also reduced the observation time and number of deaths included in our survival analysis. Finally, because our inclusion criteria required the presence of ARDS at enrollment, we are unable to make any inferences regarding associations between the comorbidities, LPV strategies, and ARDS incidence.

## Conclusion

In this prospective cohort study of patients with ARDS, we found limited data to support our hypothesis that the association between LPV and short-term survival differed according to a patient's comorbid disease state prior to ARDS onset. Future studies attempting to assess for such an effect should consider evaluating larger cohorts of ARDS patients with higher prevalences of the comorbidities of interest and use robust methods for the ascertainment of the presence or absence of the relevant comorbidities.

Figure 1: Flow of patients through study

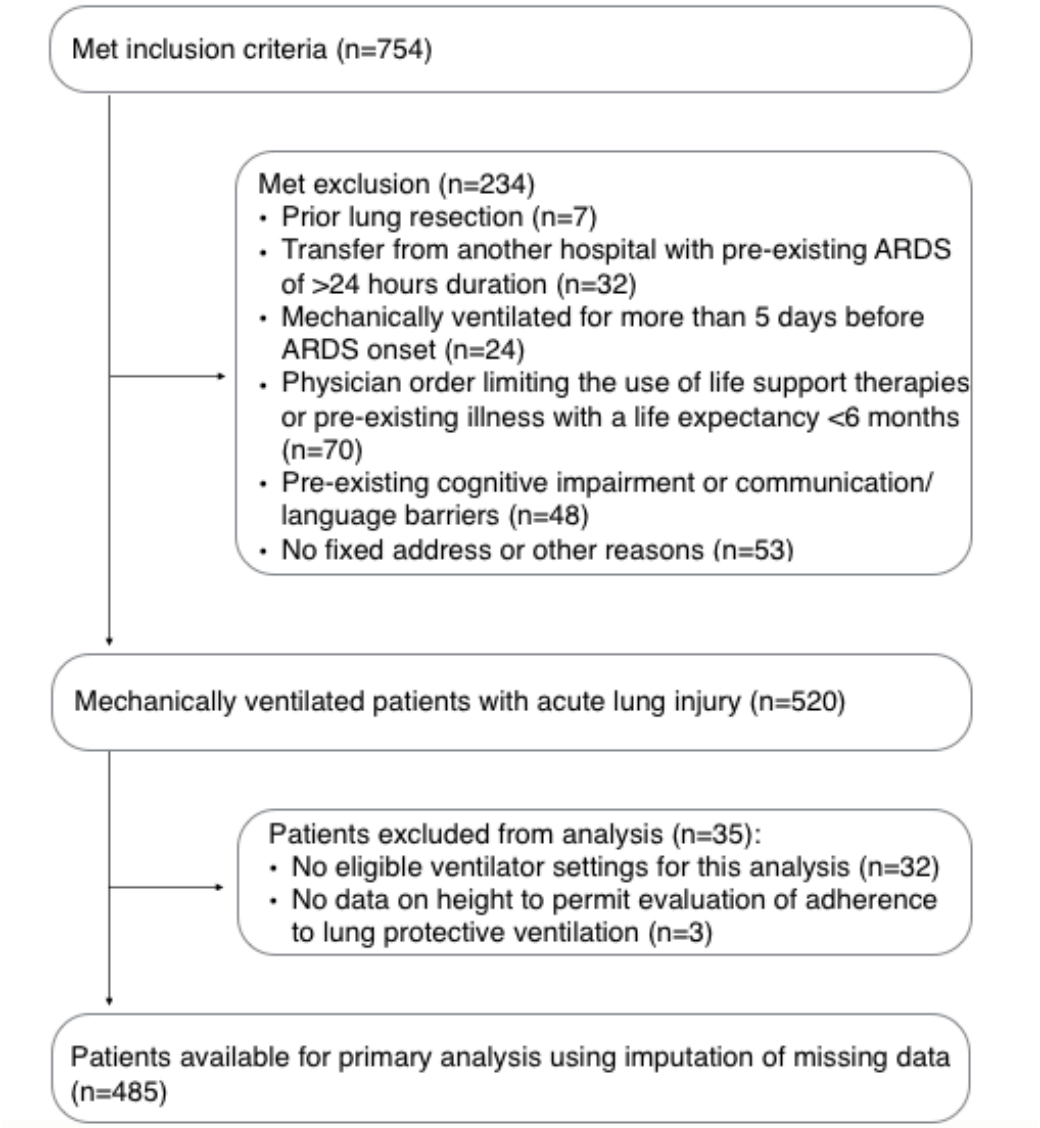

Table 1. Patient characteristics by ventilator adherence and mortality status at ICU discharge

| | All Patients (n=485) | Alive at ICU discharge (n=286) | Dead at ICU discharge (n=199) | P value | >50% LPV-Adherent* (n=156) | <= 50% LPV-Adherent* (n=329) | P value |
|---|---|---|---|---|---|---|---|
| **Median (IQR) age** | 53 (42-63) | 50 (41-60) | 55 (46-66) | 0.004 | 50 (41-59) | 53 (43-65) | 0.103 |
| **Male sex (%)** | 274 (57%) | 166 (58%) | 108 (54%) | 0.456 | 115 (74%) | 159 (48%) | <0.001 |
| **Median (IQR) Charlson comorbidity index** | 2 (1-4) | 2 (1-4) | 3 (2-5) | <0.001 | 3 (1-5) | 2 (1-4) | 0.206 |
| **Median (IQR) baseline APACHE II score** | 27 (20-33) | 24 (19-29) | 31 (25-36) | <0.001 | 27 (22-34) | 26 (20-33) | 0.559 |
| **Median (IQR) admission SOFA score** | 8 (5-12) | 8 (6-10) | 12 (9-15) | <0.001 | 10 (7-13) | 9 (6-12) | 0.145 |
| **Admission to a medical ICU (%)** | 411 (85%) | 233 (81%) | 178 (89%) | 0.02 | 149 (96%) | 262 (80%) | <0.001 |
| **Admission from emergency department (%)** | 185 (38%) | 115 (40%) | 70 (35%) | 0.296 | 60 (38%) | 125 (38%) | 0.921 |
| **Non-pulmonary sepsis as a risk factor ARDS** | 143 (30%) | 54 (19%) | 89 (45%) | <0.001 | 42 (27%) | 101 (31%) | 0.456 |
| **Underweight (BMI <18.5)** | 24 (4.9%) | 13 (5.2%) | 11 (6.2%) | 0.675 | 7 (4.9%) | 17 (6%) | 0.824 |
| **Overweight or obese (BMI >25)** | 428 (55%) | 159 (64%) | 109 (61%) | 0.685 | 72 (50%) | 196 (69%) | <0.001 |

*LPV-adherence category was calculated for each patient as: ((number of LPV-adherent ventilator settings)/ (number of LPV-eligible ventilator settings)*100)

Table 2. Patient comorbidities at admission, by ventilator adherence and mortality status at ICU discharge

| Comorbidity | All Patients (n=485) | Alive at ICU discharge (n=286) | Dead at ICU discharge (n=199) | P value | >50% LPV-Adherent‡ (n=156) | <= 50% LPV-Adherent‡ (n=329) | P value |
|---|---|---|---|---|---|---|---|
| **Excessive alcohol use†** | 119 (25%) | 68 (24%) | 51 (26%) | 0.669 | 41 (26%) | 78 (24%) | 0.573 |
| **HIV disease*** | 69 (14%) | 43 (15%) | 26 (13%) | 0.598 | 30 (19%) | 39 (12%) | 0.037 |
| **Current injection drug use¿** | 51 (11%) | 33 (12%) | 18 (9%) | 0.452 | 18 (12%) | 33 (10%) | 0.636 |
| **Rheumatologic disease*** | 36 (7.4%) | 17 (5.9%) | 19 (10%) | 0.160 | 10 (6.4%) | 26 (7.9%) | 0.711 |
| **Hematologic malignancy*** | 42 (8.7%) | 21 (7.3%) | 21 (11%) | 0.251 | 22 (14%) | 20 (6.1%) | 0.005 |
| **Diabetes*** | 112 (23%) | 64 (22%) | 48 (24%) | 0.663 | 29 (19%) | 83 (25%) | 0.108 |
| **History of moderate/ severe hepatic disease*** | 48 (9.9%) | 15 (5.2%) | 33 (17%) | <0.001 | 20 (13%) | 28 (8.5%) | 0.145 |
| **No reported chronic comorbidities** | 30 (6.2%) | 22 (7.7%) | 8 (4.0%) | 0.125 | 6 (3.9%) | 24 (7.3%) | 0.162 |

* Diseases defined using Charlson Comorbidity Index definitions (Charleson, 1987)

† Defined by documentation in the chart of current or prior alcoholism, alcohol abuse, problem drinking, alcoholic cirrhosis, or alcoholic liver disease.

¿ Defined as injection drug use documented in the medical record as "active" or within the past 30 days.

‡ LPV-adherence category was calculated for each patient as: ((number of LPV- adherent ventilator settings)/ (number of LPV-eligible ventilator settings)*100)

Table 3. Patient ICU exposures, by ventilator adherence and mortality status at ICU discharge

| | All Patients (n=485) | Alive at ICU discharge (n=286) | Dead at ICU discharge (n=199) | P value | >50% LPV-Adherent✧ (n=156) | <= 50% LPV-Adherent✧ (n=329) | P value |
|---|---|---|---|---|---|---|---|
| **Median (IQR) observations with ICU delirium** | 1 (0-4) | 2 (0-4) | 1 (0-2) | 0.002 | 1 (0-3) | 1 (0-4) | 0.496 |
| **Median (IQR) days of RASS <3** | 4 (2-9) | 4 (2-8) | 2 (1-4) | 0.309 | 5 (2-10) | 4 (2-8) | 0.144 |
| **Ever received intravenous steroids** | 329 (68%) | 157 (79%) | 169 (59%) | <0.001 | 107 (69%) | 219 (67%) | 0.680 |
| **Ever received neuromuscular blockade (%)** | 117 (24%) | 59 (21%) | 57 (29%) | 0.051 | 35 (22%) | 81 (25%) | 0.649 |
| **Median (IQR) cumulative net ICU fluid balance (L)** | 9.9 (2.8-20.4) | 9.4 (2.2-19.9) | 11.4 (4.3-21.7) | <0.001 | 6.0 (0.4-19.9) | 5.8 (0.4-15.4) | 0.529 |
| **Ever proned (%)** | 17 (3.5%) | 11 (3.9%) | 6 (3.0%) | 0.803 | 4 (2.6%) | 13 (4.0%) | 0.599 |
| **Ever received HFOV (%)*** | 57 (12) | 24 (8.4%) | 33 (17%) | 0.007 | 9 (5.8%) | 48 (15%) | 0.004 |
| **Ever received APRV (%)†** | 63 (13) | 44 (15%) | 16 (8%) | 0.017 | 8 (5.1%) | 52 (16%) | 0.001 |
| **Median days ventilation (all settings)** | 9 (5-17) | 9 (6-16) | 6 (3-12) | 0.003 | 8 (5-16) | 8 (4-14) | 0.698 |
| **Median # of LPV-eligible settings‡** | 10 (4-18) | 8 (3-17) | 9 (4-17) | 0.461 | 9 (4-18) | 9 (4-16) | 0.382 |
| **Median # of LPV-adherent settings‡** | 1 (0-6) | 1 (0-6) | 1 (0-6) | 0.644 | 6 (3-14) | 0 (0-2) | <0.001 |
| **Median initial ICU length stay (days)** | 11 (6-18) | 13 (8-20) | 7 (3-13) | <0.001 | 10 (3-10) | 11 (6-17) | 0.330 |

*HFOV = high frequency oscillatory ventilation †APRV = airway pressure release ventilation ‡LPV= lung protective ventilation Patients were defined as eligible for lung protective ventilation if mechanical ventilation was delivered via an tracheostomy or endotracheal tube with a positive end expiratory pressure >5 cm water or fraction of inspired oxygen >= 0.50. HFOV and APRV modes were not considered eligible for assessment of adherence to an LPV strategy.
✧LPV-adherence category was calculated for each patient as: ((number of LPV- adherent ventilator settings)/ (number of LPV-eligible ventilator settings)*100)

Table 4. Bivariable and Multivariable Cox Regression Model

| | Bivariable Hazard Ratio* (95% Confidence Interval) | P value‡ | Multivariable hazard ratio* (95% Confidence Interval) | P value‡ |
|---|---|---|---|---|
| **Age (per year)** | 1.02 (1.01-1.26) | <0.001 | 1.03 (1.02-1.04) | <0.001 |
| **Female sex** | 1.00 (0.81-1.36) | 0.736 | 1.14 (0.83-1.56) | 0.422 |
| **Underweight (BMI < 18.5)** | 1.44 (0.83-2.47) | 0.192 | 1.15 (0.61-2.15) | 0.667 |
| **Overweight (BMI > 25)** | 0.85 (0.65-1.13) | 0.266 | 0.79 (0.57-1.09) | 0.145 |
| **Admission from ED** | 0.96 (0.73-1.26) | 0.782 | 1.99 (1.39-2.86) | <0.001 |
| **Admission to a MICU** | 1.70 (1.13-2.55) | 0.011 | 2.96 (1.60-5.47) | 0.001 |
| **Non-pulmonary sepsis as risk factor** | 2.27 (1.75-2.96) | <0.001 | 1.58 (1.16-2.15) | 0.004 |
| **Admission Charlson Index** | 1.06 (1.01-1.11) | <0.01 | 0.98 (0.90-1.08) | 0.740 |
| **Admission APACHE II Score** | 1.06 (1.05-1.08) | <0.001 | 1.04 (1.02-1.06) | <0.001 |
| **Admission SOFA Score** | 1.15 (1.11-1.18) | <0.001 | 1.07 (1.02-1.13) | 0.004 |
| **Hospital Site 2 (vs. 1)** | 0.94 (0.69-1.26) | 0.665 | 1.20 (0.80-1.78) | 0.377 |
| **Hospital sites 3 & 4 (vs. 1)** | 0.60 (0.44-0.84) | 0.003 | 1.07 (0.64-1.77) | 0.800 |

*Hazard ratio > 1.0 represents increased of death during index ICU stay. Multivariable model includes terms for all seven comorbidities of interest simultaneously.

‡P values adjusted for within-patient correlation using robust variance estimate.

Table 4 (continued). Bivariable and Multivariable Cox Regression Model

| | Bivariable Hazard Ratio* (95% Confidence Interval) | P value‡ | Multivariable Hazard Ratio* (95% Confidence Interval) | P value‡ |
|---|---|---|---|---|
| **HIV or AIDS✢** | 0.83 (0.56-1.22) | 0.346 | 0.95 (0.49-1.83) | 0.876 |
| **Current or prior excessive alcohol use†** | 1.04 (0.76-1.42) | 0.796 | 0.96 (0.59-1.55) | 0.863 |
| **Current injection drug use¿** | 0.75 (0.46-1.22) | 0.246 | 1.08 (0.53-2.19) | 0.827 |
| **Rheumatologic Disease✢** | 1.70 (1.10-2.65) | 0.018 | 2.65 (1.40-5.02) | 0.003 |
| **Hematologic malignancy✢** | 1.14 (0.77-1.70) | 0.513 | 0.77 (0.50-1.17) | 0.217 |
| **Moderate/ severe liver disease✢** | 2.37 (1.69-3.32) | <0.001 | 0.80 (0.44-1.46) | 0.474 |
| **Diabetes✢** | 1.10 (0.81-1.48) | 0.539 | 0.45 (0.20-1.02) | 0.056 |

*Hazard ratio > 1.0 represents increased of death during index ICU stay. Multivariable model includes terms for all seven comorbidities of interest simultaneously.

‡P values adjusted for within-patient correlation using robust variance estimate

✢ Diseases defined using to Charlson Comorbidity Index definitions (Charlson, 1987)

† Defined by documentation in the chart of current or prior alcoholism, alcohol abuse, problem drinking, alcoholic cirrhosis, or alcoholic liver disease.

¿ Defined as injection drug use documented in the medical record as "active" or within the past 30 days.

Table 4 (continued). Bivariable and Multivariable Cox Regression Model

| | Bivariable Hazard Ratio✢ (95% Confidence Interval) | P value‡ | Adjusted hazard ratio✢ (95% Confidence Interval) | P value‡ |
|---|---|---|---|---|
| **Cumulative number of 12 hour LPV-adherent periods*** | 1.02 (1.00-1.03) | 0.009 | 0.96 (0.93-1.00) | 0.041 |
| **Duration of mechanical ventilation (per day)** | 1.01 (1.00-1.02) | 0.003 | 0.94 (0.91-0.98) | 0.001 |
| **Cumulative number of 12 hour periods proned** | 1.05 (0.97-1.14) | 0.213 | 1.04 (1.02-1.06) | <0.001 |
| **Cumulative number of 12 hour periods paralyzed** | 1.00 (1.00-1.01) | 0.255 | 1.03 (0.98-1.90) | 0.209 |
| **Cumulative number of 12 hour periods on APRV settings** | 1.02 (1.00-1.03) | 0.014 | 0.95 (0.92-0.97) | <0.001 |
| **Cumulative number of periods on HFOV settings** | 1.05 (1.02-1.03) | 0.003 | 0.95 (0.91-0.99) | 0.024 |
| **Cumulative number of days with RASS <-3** | 1.02 (1.01-1.04) | <0.001 | 1.04 (1.01-1.06) | 0.003 |
| **Cumulative number of days of delirium** | 1.04 (1.00-1.08) | 0.079 | 1.03 (0.94-1.12) | 0.527 |
| **Cumulative number of days receiving intravenous steroids** | 1.04 (1.03-1.05) | <0.001 | 1.09 (1.05-1.13) | <0.001 |
| **Cumulative intravenous steroid dose (per 50 mg prednisone-equivalents)** | 1.00 (1.00-1.00) | 0.151 | 1.00 (1.00-1.00) | 0.506 |
| **Cumulative mean PEEP setting (per 1 cm water)** | 1.18 (1.13-1.23) | <0.001 | 1.31 (1.23-1.39) | <0.001 |
| **Cumulative mean PaO2/FiO2 ratio (per 10 units)** | 0.97 (0.95-0.98) | <0.001 | 0.96 (0.93-0.98) | 0.001 |
| **Cumulative observations of arterial pH <7.25†** | 1.00 (1.00-1.00) | 0.005 | 1.00 (1.00-1.01) | 0.257 |
| **Cumulative mean static compliance (per 10 unit increment)** | 0.95 (0.87-1.04) | 0.290 | 0.71 (0.60-0.83) | <0.001 |
| **Mean daily respiratory rate, per 1 breath/min** | 1.00 (0.98-1.02) | 0.863 | 0.95 (0.92-0.98) | 0.001 |
| **Cumulative net fluid (per liter)** | 2.28 (2.03-2.55) | <0.001 | 1.04 (1.03-1.05) | <0.001 |

✢Hazard ratio > 1.0 represents increased of death during index ICU stay. Multivariable model includes terms for all seven comorbidities of interest simultaneously. ‡P values adjusted for within patient correlation using robust variance estimate. *Adjusted for cumulative duration of mechanical ventilation.
†From blood gas measurements abstracted twice daily, when available, from the medical record.

Table 5. Multivariable Cox Regression Model with Statistical Interaction of Comorbidity and LPV-adherence✦

| Comorbidity | Comorbidity Prevalence (n=485) | P-value‡ for statistical interaction of LPV and co-morbidity in this model | Adjusted Hazard Ratio (95% Confidence Interval) for each additional 12-hour LPV-adherent period✢ | | | |
|---|---|---|---|---|---|---|
| | | | Patients without the co-morbidity | P value‡ | Patients with the comorbidity, | P value‡ |
| **HIV or AIDS*** | 69 (14%) | 0.97 | 0.96 (0.93-1.00) | 0.07 | 0.96 (0.91-1.02) | 0.214 |
| **Current or prior excessive alcohol use†** | 119 (25%) | 0.222 | 0.97 (0.93-1.00) | 0.056 | 0.92 (0.85-0.99) | 0.03 |
| **Current injection drug use¿** | 51 (11%) | 0.746 | 0.96 (0.93-0.99) | 0.045 | 0.95 (0.85-1.06) | 0.336 |
| **Rheumatologic disease*** | 36 (7.4%) | 0.074 | 0.96 (0.93-1.00) | 0.051 | 0.95 (0.83-1.10) | 0.533 |
| **Hematologic malignancy*** | 42 (8.7%) | 0.039 | 0.96 (0.93-1.00) | 0.035 | 1.03 (0.94-1.12) | 0.580 |
| **Moderate/ severe liver disease*** | 48 (9.9%) | 0.899 | 0.97 (0.94-1.00) | 0.059 | 0.89 (0.82-0.97) | 0.009 |
| **Diabetes*** | 112 (23%) | 0.164 | 0.98 (0.95-1.01) | 0.266 | 0.90 (0.84-0.97) | 0.006 |

✦ LPV-adherence*comorbidity interaction terms added to the model individually

‡P values adjusted for within patient correlation using robust variance estimate.

✢Hazard ratio > 1.0 represents increased of death during index ICU stay. Multivariable model includes terms for all seven comorbidities of interest simultaneously.

*Diseases defined using to Charlson Comorbidity Index definitions (Charlson, 1987)

*† Defined by documentation in the chart of current or prior alcoholism, alcohol abuse, problem drinking, alcoholic cirrhosis, or alcoholic liver disease

¿ Defined as injection drug use documented in the medical record as "active" or within the past 30 days.

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